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REMARKS

Claims 1, 3, 4, 7-11, 13-17, 20-22 and 26-29 are rejected.

Claims 5 and 6 have been canceled in favor of new claim 31.

Claims 21, 22 and 24 have been canceled.

Claims 17, 23 and 30 have been amended.

Claims 5, 6, 23, 24 and 30 were objected to as being dependent upon a rejected claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Accordingly Claims 5 and 6 are canceled in favor of new claim 31 incorporating the limitations of Claims 5 and 6 in part (c) i. Additionally Claims 21, 22 and 24 have been canceled and the limitations of these claims incorporated into amended Claim 17.

No new matter has been added.

Rejections Under 35 U.S.C. §103(a)

a. Claims 1, 3, 7-11, 15 and 16 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Perkins et al. (U.S. Patent Application Publication No. 2002/0151058, of record) in view of Yu et al. (of record) and further in view of Prideaux et al. (U.S. Patent No. 6,472,183) for reasons of record. Applicants traverse.

It is well settled that in order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP 2143.

Applicants remarks opposite this maintained rejection made in the response mailed 11/17/2006 are relevant and are hereby incorporated by reference. Additionally, Applicants submit that Perkins is an inappropriate reference under 35 USC § 103 for the reasons argued below.

In the instant application, the claimed method is based on the use of multiple, linear DNA fragments having very short regions of homology for prokaryotic chromosomal engineering using the λ-Red recombination system. The Applicant respectfully asserts that one of ordinary skill in the art would not consider the exemplified teachings of the Perkins et al. reference as relevant to the claimed invention. As such, the Applicant respectfully asserts the *prima facie* case of obviousness based on the use of the Perkins et al. reference is not appropriate, and therefore, not supported.

The Applicant provides the following reasons as to why the Perkins et al. reference, the primary reference used as a foundation for all of the claims rejections under 35 U.S.C.

§103, should not be considered as an analogous or enabling reference suitable for supporting the Examiner's case of *prima facie* obviousness.

The Applicant respectfully asserts that the Perkins et al. reference is not an enabling reference nor should it be considered a valid reference as it is not analogous to the claimed invention. The Applicant respectfully asserts that the Examiner has taken excerpts from the Perkins et al. reference to form a *prima facie* obviousness rejection ex post facto. However, the Applicant would like to bring to the Examiner's attention that one of ordinary skill in the art needs to consider all of the teachings of the Perkins et al. reference in the context of the entire reference. "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984) (...). MPEP 2141.02 (VI). When one of ordinary skill in the art examines the teachings of the Perkins et al. reference in detail, it is clear that one of ordinary skill in the art would not consider the reference as relevant to the claimed invention.

The Applicant respectfully asserts that the Perkins et al. reference illustrates homologous recombination using linear, double stranded DNA molecules (linearized plasmids) in a eukaryotic host cell (yeast). All of the working examples are in a eukaryotic host cell (yeast). The mechanisms of double strand break GAP-repair mediated homologous recombination in yeast is well-known in the art and is non-analogous (both structurally and functionally) to the λ-Red recombination system. The Applicant respectfully asserts that one of ordinary skill in the art would not consider a reference that only exemplifies GAP-repair mediated homologous recombination in eukaryotic cells (for the purpose of creating eukaryotic expression vector) as relevant to the λ-Red mediated chromosomal engineering in a prokaryotic cell. The Applicant respectfully asserts that one of ordinary skill in the art would not have considered nor looked towards the Perkins et al. reference at the time the claimed invention was made to obtain the claimed invention.

E coli

Specifically, the Applicant would like to respectfully bring to the Examiner's attention the following elements that would direct one of ordinary skill in the art away from considering the Perkins et al. reference in any way relevant to a method based on multiple linear nucleic acid fragment chromosomal engineering in a prokaryotic cell (E. coli) using λ-Red mediated homologous recombination:

1. Prokaryotic and eukaryotic recombination systems are vastly different. All of the working examples in the Perkins et al. reference are based on a yeast cell model using GRIPP (gap repair with an inverse PCR-amplified plasmid). Clearly, GRIPP technology is dependent upon the endogenous GAP repair system known to residue in yeast. No prokaryotic host cells are exemplified or sufficiently described as to enable one of ordinary skill in the art to conclude that the exemplified process (double strand break GAP repair mediated eukaryotic plasmid synthesis) is in any way relevant to the claimed process or method in the instant

application. Eukaryotic meiotic recombination involves a complex set of proteins often referred to as the RAD52 epistasis group. (for example, see Symington, L., *Microbiol. Molec. Biol. Rev.* 66(4):630-670 (2002)). The number of proteins involved, as well as the structure of the proteins, is vastly different when compared to the λ-Red recombination system;

2. It is well-known that linear, double stranded DNA molecules (such as linearized plasmids) can be used for in vivo transformation in a eukaryotic cell (yeast). The endogenous double strand break (DSB) gap repair mechanism in yeast will efficiently restore double strand breaks via homologous recombination. (for example, see Kunes et al., *J. Mol. Biol.* 1985 184:375-387; Orr-Weaver, T. and Szostak, J., *PNAS* 1983 80:4417-4421). Kunes et al. (a 20-plus year old reference) teaches transformation of yeast with linearized plasmid DNA using the endogenous double strand break repair system. Homologous transformation using yeast GAP repair involves numerous gene products that are not functional in *E. coli* and are structurally different to the elements of the λ-Red recombination system;

3. No working examples nor an enabling description is provided showing that the process illustrated by the Perkins et al. reference is applicable to a prokaryotic system nor is there any reference to λ-Red mediated chromosomal engineering;

4. All of the examples in the Perkins et al. reference illustrate the use of GRIPP that relies on the endogenous GAP repair system in yeast to prepare eukaryotic expression plasmids only. The Applicant respectfully asserts the different end use, as well as the difference in the elements involved in eukaryotic double strand break repair further supports the assertion that one of ordinary skill in the art would not consider this reference as relevant to the claimed method in the instant application; and

5. Biotechnology is considered an unpredictable art, even when using structurally homologous elements. The differences in cellular organization and intracellular environment between eukaryotic and prokaryotic organisms, the differences in the structures of the elements involved in homologous recombination, as well as the unpredictable nature of the art, would not lead one of ordinary skill in the art to consider the Perkins et al. reference, as a whole, to be an appropriate and enabling reference that one could look towards to derive the claimed invention. Given all of the significant differences between the Perkins et al. system and the claimed method in the instant application, one ordinary of skill in the art would not believe that the system taught by the Perkins et al. reference would have any reasonable expectation of success in *E. coli*, especially for a different intended purpose (i.e. multifragment chromosomal engineering).

In view of the above arguments and the arguments of record Applicant submits that, the Examiner has not established a *prima facie* case of obviousness of the claims in this application, in that the skilled person would not have been motivated to combine the yeast based teachings of Perkins with Yu or Prideaux and would have had no reasonable

expectation of success. Accordingly, the Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejections directed to claims 1, 3, 7-11, 15 and 16.

b. Claims 1, 3, 4, 7, 8, 11, 13-17, 20-22 and 26-29 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Perkins et al. (of record) in view of Yu et al. (of record) and further in view of Welch et al. (U.S. Patent Application Publication No. 2002/0187544) as evidenced by Guzman et al. (J. Bacteriol., 177(14): 4121-4130 (1995)). Applicants traverse.

Applicants reiterate that Perkins does not make the present invention obvious in as much as the skilled person would have no motivation to combine Perkins with Yu or Welch and would have no reasonable expectation of success as argued above.

CONCLUSION

Claims 5, 6, 23, 24 and 30 were objected to as being dependent upon a rejected claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The limitations of Claims 5 and 6 are now incorporated into new claim 31. Claim 17 now includes the limitations of Claims 23 and 24 and Claim 30 is now dependant on amended Claim 17 or new claim 31. In view of these amendments Applicants submit that the subject matter contained in original Claims 5, 6, 23, 24 and 30 is in condition for allowance. In the instance where Claim 31 is deemed allowable, Applicants reserve the right to include dependant claims to Claim 31 commensurate in scope with the subject matter of original Claims 3-16.

In view of the arguments and remarks presented above, Applicants respectfully request withdrawal of all rejections and allowance of all claims remaining in the case.

Should the Examiner wish to discuss any issues involved in this application, the Examiner is respectfully invited to contact the undersigned at the telephone exchange set forth below. Should there be any fee due in connection with the filing of this Amendment, please charge such fee to Deposit Account No. 04-1928 (E. I. du Pont de Nemours and Company).

Respectfully submitted,

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